PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC-21016093	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/SE2004/001644	International filing date *(day/month/year)* 10-11-2004	Priority date *(day/month/year)* 19-12-2003
International Patent Classification (IPC) or national classification and IPC See Supplemental Box		
Applicant CMS Contrast AB et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☒ Box No. II Priority
   - ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☒ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05-07-2005	06-03-2006
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88	Authorized officer Malin Söderman/MP Telephone No. +46 8 782 25 00

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Cover sheet

International patent classification (IPC)

A61K 49/06 (2006.01)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☐ the international application in the language in which it was filed

☐ a translation of the international application into _____ ,
which is the language of a translation furnished for the purposes of:

☐ international search (Rules 12.3(a) and 23.1(b))

☐ publication of the international application (Rule 12.4(a))

☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

☐ the international application as originally filed/furnished

☒ the description:

pages 1-14 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

pages _____ as originally filed/furnished

pages* _____ as amended (together with any statement) under Article 19

pages* 15-17 received by this Authority on 01-11-2005

pages* _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to the sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to the sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. II Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed (Rule 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 66.7(b)).

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rule 64.1). Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

The priority is considered valid. Document Thomsen et al, "Increased Manganese Concentration in the Liver after Oral Intake", Academic Radiology, January 2004, vol. 11, no. 1, pages 38-44, is therefore of no relevance.

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 21

because:

☒ the said international application, or the said claims Nos. 21
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in the Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-20	YES
	Claims		NO
Inventive step (IS)	Claims	1-20	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-20	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents:
D1: WO9811922 A2
D2: WO9702842 A1
D3: WO9605867 A2
D4: US4863898 A
D5: US6015545 A

The claimed invention relates to the use of a physiologically acceptable manganese (II) compound and an uptake promoter in the form of one or more amino acids for the manufacture of an MRI contrast composition for oral administration and MRI examination of the liver, in a ratio of Mn to promoter higher than that at which coordination compounds between Mn and promoter are formed to a substantial degree; an MRI contrast medium composition for such use; an MRI contrast medium kit; and a method for imaging of a mammalian liver using such contrast medium composition.

D1 describes an MRI contrast medium composition for use in a method for functional imaging of the gastrointestinal tract, see abstract. D1 also describes a method for rectal administration for obtaining images of the liver, see page 7, lines 5-18. In D1, manganese may be used in combination with a promoter, see page 8, line 14-page 9, line 25. The molar ratio of manganese to uptake promoter can be 1:0.2-1:50 or 1:1.5-1:5. The promoter can be, for example, alanine or aspartic acid.
.../...

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of: Box V

D2 describes a contrast medium that contains as active ingredient a manganese compound and an uptake promoter, see abstract. According to D2, 100 micromole/kg manganese(II)chloride tetrahydrate and 300 micromole/kg promoter can be used, see page 12.

D3 involves a contrast medium composition comprising a physiologically tolerable manganese compound and an uptake promoter and a physiologically tolerable carrier or excipient. The composition has a manganese concentration of 0.3 mM or is in a dosage unit form containing 300 micromole manganese, see abstract.

D4 relates to amino acid chelates having a ligand to divalent metal mole ratio of at least 2:1 for delivery to one or more specific tissue sites within a mammal, see abstract.

D5 describes a composition for use as a contrast medium being particularly suitable for imaging of the stomach, liver, bile duct and gall bladder, said composition comprising as an active ingredient a physiologically acceptable manganese compound and an uptake promoter, see abstract.

The cited documents represent the general state of the art.
The invention defined in claims 1-20 is not disclosed by any of these documents.
The cited prior art does not give any indication that would lead a person skilled in the art to the claimed ratio of manganese to promoter. Therefore, the claimed invention is not obvious to a person skilled in the art.
Accordingly, the invention defined in claims 1-20 is novel and is considered to involve an inventive step. The invention is industrially applicable.

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Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*

Thomsen et al, "Increased Manganese Concentration in the Liver after Oral Intake", Academic Radiology, January 2004, vol. 11, no. 1, pages 38-44,

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

PCT/SE 2004/001644
01-11-2005
10/583317
AP3 Rec'd PCT/PTO 15 JUN 2006

CLAIMS

1. The use of a physiologically acceptable manganese (II) compound and an uptake promoter in the form of one or more amino acids for the manufacture of an MRI contrast composition for oral administration and MRI examination of the liver, in a ratio of Mn to promoter higher than that at which coordination compounds between Mn and promoter are formed to a substantial degree, wherein the molar ratio of Mn to promoter is in the range of from 2:3 to 3:1.

2. The use according to claim 1, wherein said ratio is in the range of from 1:1 to 3:1.

3. The use according to claim 2, wherein said ratio is in the range of from 2:1 to 3:1.

4. The use according to any one of the preceding claims, wherein the dosage of manganese is in the range of from 25 to 150 µmol/ kg body weight.

5. The use according to claim 4, wherein the dosage of manganese is in the range of from 50 to 125 µmol/ kg body weight.

6. The use according to claim 5, wherein the dosage of manganese is in the range of from 50 to 100 µmol/ kg body weight.

7. The use according to any one of the preceding claims, wherein the uptake promoter is selected from the group consisting of alanine, valine, leucine, tryptophan, methionine, isoleucine, proline, phenylalanine, serine, glycine, threonine, cysteine, asparagine, glutamine, tyrosine, aspartic acid, glutamic acid, arginine, lycine and histidine.

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8. The use according to claim 7, wherein said promoter is selected from neutral amino acids including asparagine and aspartic acid.

9. The use according to claim 8, wherein said promoter is L-alanine.

10. An MRI contrast medium composition for oral administration for examination of the liver comprising as an active ingredient a physiologically acceptable manganese (II) compound and an uptake promoter comprising one or more amino acids wherein Mn and the promoter are used in a molar ratio higher than that at which coordination compounds between Mn and promoter are formed to a substantial degree, wherein the molar ratio of Mn to promoter is in the range of from 2:3 to 3:1.

11. A composition according to claim 10, wherein said ratio is in the range of from 1:1 to 3:1.

12. A composition according to claim 11, wherein said ratio is in the range of from 2:1 to 3:1.

13. A composition according to any one of claims 10 to 12, wherein the dosage of manganese is in the range of from 25 to 150 µmol/ kg body weight.

14. A composition according to claim 13, wherein the dosage of manganese is in the range of from 50 to 125 µmol/ kg body weight.

15. A composition according to claim 14, wherein the dosage of manganese is in the range of from 50 to 100 µmol/ kg body weight.

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16. A composition according to any one of claims 10 to 15, wherein the uptake promoter is selected from the group consisting of alanine, valine, leucine, tryptophan, methionine, isoleucine, proline, phenylalanine, serine, glycine, threonine, cysteine, asparagine, glutamine, tyrosine, aspartic acid, glutamic acid, arginine, lycine and histidine.

17. A composition according to claim 16, wherein said promoter is selected from neutral amino acids including asparagine and aspartic acid.

18. A composition according to claim 17, wherein said promoter is L-alanine.

19. An MRI contrast medium kit comprising a first container accomodating a physiologically acceptable manganese (II) compound, and a second container accomodating an uptake promoter comprising one or more amino acids, and optionally, instructions for the use of the kit, the molar ratio of Mn to promoter being within the range of 2:3 to 3:1.

20. A kit according to claim 19, wherein said molar ratio, the dosage of manganese and/or said uptake promoter is (are) as defined in any one of claims 11 to 18.

21. A method for MRI of a mammalian liver using an MRI contrast medium composition according to any one of claims 10 to 18, said method comprising oral administration of an effective amount of said contrast medium composition.